



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/155,252	09/21/1998	RONALD MARK EVANS	SALK1470-2	8370

7590

09/05/2003

STEPHEN E REITER
FOLEY & LARDNER
P O BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER

BUNNER, BRIDGET E

ART UNIT PAPER NUMBER

1647

DATE MAILED: 09/05/2003

32

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicant(s)

09/155,252

Applicant(s)

EVANS ET AL.

Examiner

Bridget E. Bunner

Art Unit

1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 May 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 16,18-20 and 27-45 is/are pending in the application.
- 4a) Of the above claim(s) 29-35 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 16,18-20 and 43 is/are allowable.
- 6) ☒ Claim(s) 27,28,36,37,39-42,44 and 45 is/are rejected.
- 7) ☒ Claim(s) 38 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

Art Unit: 1647

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 27 May 2003 (Paper No. 31) has been entered in full. Claims 16, 18-20, 27-28, and 43-45 are amended. Claims 17 is cancelled.

This application contains claims 29-35 drawn to a non-elected invention. Since applicant had received an action on the merits for the originally presented invention, this invention was constructively elected by original presentation for prosecution on the merits. Please see pg 2 of previous Office Action (Paper No. 30, 26 February 2003). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's traversal of the withdrawal of claims 29-35 from consideration appears moot since Applicant has received an action on the merits for the originally presented invention. If Applicant wishes to pursue the matter further, a petition should be filed in accordance with 37 CFR 1.144.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 16, 18-20, 27-28, 36-45 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to claims 17-20, 38, and 43-45 as being dependent upon a rejected base claim as set forth at pg 3 of the previous Office Action (Paper no. 30, 26 February 2003) is *withdrawn in part* in view of the amendment to claim 16 (27 May 2003; Paper No. 31). Please see section on Claim Objections, below.

Art Unit: 1647

2. The rejection of claims 16 and 27-28 under 35 U.S.C. § 102(b) as set forth at pg 3-4 of the Office Action of 26 February 2003 (Paper No. 30) is *withdrawn in part* in view of the amendment to claim 16 (27 May 2003, Paper No. 31). Please see section on 35 U.S.C. § 102(b), below.

Oath/Declaration

3. The objection to the declaration regarding the issue of not identifying the post office address of each inventor is maintained and held in abeyance until allowable subject matter is identified (see the Office Action of 15 August 2001, Paper No. 17).

Claim Objections

4. Claim 38 is objected to as being dependent upon a rejected base claim.

Claim Rejections - 35 USC § 102

5. Claims 27 is rejected under 35 U.S.C. 102(b) as being anticipated by Marcus et al. (Proc Natl Acad Sci USA 90: 5723-5727, 1993).

Applicant's arguments (Paper No. 31, 27 May 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that regarding claim 27, this claims is distinguishable over Marcus et al. by requiring contacting the test cells with at least two compounds. Applicant argues that claim 27 requires contacting the cells with a test compound and at least one additional compound that is a PPAR- γ agonist. Applicant states that Marcus et al. does not teach or suggest the use of a second compound to determine the activity of the test compound.

Applicant's arguments have been fully considered but are not found to be persuasive. Briefly, Marcus et al. teaches cotransfecting COS-1 cells with a PPAR- γ receptor expression

Art Unit: 1647

vector and a reporter vector and contacting the cells with ciprofibrate, or Wy-14,643, wherein the substances caused an increase or decrease in the level of luciferase reporter protein (pg 5724-5725; pg 5726; Figures 1 and 6). However, Marcus et al. also teaches that COS cells may contain endogenous factors that activate mouse and rat PPAR, but not *Xenopus* PPAR (pg 5725, lines 1-3 and first and second full paragraphs). Therefore, Marcus et al. does teach a method of testing a compound for its ability to regulate transcription-activating effects of a PPAR- γ comprising assaying for changes in the level of reporter gene as a result of contacting cells containing said receptor and reporter vector with said compound and in the further presence of at least one additional compound that is a PPAR- γ antagonist or agonist.

Claim Rejections - 35 USC § 103

7. Claims 36-37 and 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webster et al. (Cell 54:199-207, 1988) in view of Greene et al. (U.S. Patent 6,200,802).

Applicant asserts that Webster et al. merely uses known receptor activators in a mechanistic study to localize the activation domains of the human estrogen or glucocorticoid receptors. Applicant argues that Webster et al. does not teach or suggest the use of GAL4-PPAR- γ chimeras to test compounds for PPAR- γ regulation. Applicant submits that Greene et al. is unable to cure the deficiencies of Webster et al. because it also does not teach or suggest the use of GAL4-PPAR- γ chimeras to test compounds for PPAR- γ regulation. Applicant indicates that Greene et al. discloses the identification of PPAR- γ receptors. Applicant argues that both references are completely silent regarding the identification of PPAR- γ modulators using a bioassay as defined in claim 36. Applicant asserts that the study of receptor activation in the presence of a known receptor ligand (Webster et al.) is clearly not equivalent to the use of

Art Unit: 1647

receptor activation for the identification of novel PPAR- γ modulators. Applicant states that Webster et al. specifically uses known activators to study receptor activation because the goal of Webster is to localize functional activation domains. Applicant contends that the presence of an unknown or test compound would be completely antithetical to the desired goal because a change in activation could no longer be attributed solely to the receptor domains being studied to localize the activation domain. Applicant concludes that the present invention focuses on identifying novel PPAR- γ modulators, rather than identifying or characterizing the receptor and only the Applicants have used chimeric GAL4-PPAR- γ receptors in the identification of novel compounds that regulate PPAR- γ .

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, the Webster et al. reference and Greene et al. reference in combination each the identification of PPAR- γ modulators using a bioassay as recited in claims 36-37 and 39-42. As discussed in the previous Office Action, Webster et al. teaches a method of testing a compound for its ability to regulate transcription-activating effects of estrogen and glucocorticoid receptors by assaying for the changes in the level of CAT reporter protein present as a result of contacting cells containing GAL4 chimeric estrogen/glucocorticoid receptors and a reporter vector with the compound (pg 200, col 2; Figure 2-3; pg 202, last ¶ of col 2 through 203). Webster et al. discloses GAL4 chimeric estrogen(ER)/glucocorticoid (GR) receptor expression vectors that comprise DNA that encodes amino acids 1-74 or amino acids 1-174 of the DNA binding domain of GAL4 and a region containing the hormone-binding domain of human ER or GR (pg 200, col 2; Figure 5). Webster teaches substituting the native DNA binding domain of PPAR- γ with the DNA encoding the GAL4 DNA binding domain (pg 199-201). Webster et al also teaches a

Art Unit: 1647

reporter vector that comprises rabbit β -globin promoter, two synthetic 17-mer GAL4 DNA binding sites, and a DNA segment that encodes the CAT reporter protein (pg 200, col 2; Figure 3(A)). Webster et al. teaches cotransfecting HeLa cells with the receptor expression vector and reporter vector and contacting the cells with hormones and anti-hormones wherein the substances caused an increase or decrease in the level of CAT reporter protein (pg 202-203; Figure 3(B)-3(C)). Although Webster et al. does not teach a GAL4 chimeric PPAR- γ receptor expression vector, Greene et al. teaches the nucleic acid sequence and amino acid sequence of the human PPAR- γ receptor. Greene et al. also discloses several domains of PPAR- γ , such as the D domain or ligand binding domain (col 14, Figure 1). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the GAL4 chimeric receptor/reporter vector method for testing the transcription activation of a compound as taught by Webster et al. by utilizing the PPAR- γ receptor as taught by Greene et al.

Furthermore, as mentioned above, Applicant states that Webster et al. specifically uses known activators to study receptor activation and that the presence of an unknown or test compound would be opposed to the desired goal in the method of Webster et al. However, the feature upon which Applicant relies (i.e., contacting cells with an unknown compound), is not recited in the rejected claims. The rejected claims only recite "a method for testing a compound for its ability to regulate transcription-activating effects of a PPAR- γ ".

New Claim Rejections - 35 USC § 103

8. Claim 28 is rejected under 35 U.S.C. 102(b) as being anticipated by Ikonen et al. (Endocrinology 135: 1359-1366, 1994) in view of Marcus et al. (Proc Natl Acad Sci USA 90: 5723-5727, 1993).

Ikonen et al. teaches co-transfecting CV-1 cells with pSG5-rAR (rat androgen receptor expression vector) and pMMTV-CAT reporter (pg 1360; col 1; pg 1361, last ¶; pg 1362, col 1). Ikonen et al. discloses that after transfection, the cells receive medium supplemented with testosterone and 8-Br-cAMP or Casodex (abstract; Figure 1). Ikonen et al. teaches that the concomitant presence of Casodex with testosterone blunted the androgen-elicited activation of the CAT reporter construct to 15-20% of that with testosterone alone (pg 1362, col 1). Ikonen et al. indicates that Casodex behaved like a pure androgen antagonist (pg 1362, col 1). Therefore, Ikonen et al. teaches testing a compound for its ability to regulate transcription-activating effects of a receptor comprising assaying for changes in the level of reporter protein present as a result of contacting cells containing the receptor and reporter vector with the compound and further in the presence of at least one additional compound that is a receptor antagonist.

Ikonen et al. does not teach a receptor expression vector comprising a DNA segment encoding PPAR- γ .

Marcus et al. teaches method of testing a compound for its ability to regulate transcription-activating effects of the PPAR- γ receptor by assaying for the changes in the level of luciferase reporter protein present as a result of contacting cells containing PPAR- γ and a reporter vector with the compound. Marcus et al. discloses a PPAR- γ receptor expression vector that comprises DNA encoding *Xenopus* PPAR- γ (pg 5724, ¶ 1). Marcus et al also teaches a reporter vector entitled, pHD(x3)luc, that comprises a rat enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase (HD) promoter, 3 tandem copies of the HD peroxisome proliferator-responsive element (PPRE), and a luciferase reporter gene (pg 5723, last ¶). Marcus et al. discloses a second reporter vector, entitled pAOx(x2)luc, that comprises a rat fatty acyl-CoA

Art Unit: 1647

oxidase (AOx) promoter, 2 tandem copies of the rat AOx PPRE, and a luciferase reporter gene (pg 5723, last ¶). Marcus et al. teaches cotransfecting COS-1 cells with the receptor expression vector and a reporter vector and contacting the cells with ciprofibrate, or Wy-14,643, wherein the substances caused an increase or decrease in the level of luciferase reporter protein (pg 5724-5725; pg 5726; Figures 1 and 6).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method for testing the transcription activation of a compound as taught by Ikonen et al. by utilizing the PPAR- γ receptor expression vector and reporter construct as taught by Marcus et al. The person of ordinary skill in the art would have been motivated to make that modification because peroxisome receptors are essential for lipid metabolism and may play a role in cancer cell growth and differentiation (Marcus et al., pg 5723, ¶ 1). The person of ordinary skill in the art reasonably would have expected success because similar methods were already being performed to discover the transcription activating effects of various compounds on receptors at the time the invention was made. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

9. Claims 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webster et al. (Cell 54:199-207, 1988) in view of Greene et al. (U.S. Patent 6,200,802) and Ikonen et al. (Endocrinology 135: 1359-1366, 1994).

Webster et al. teaches a method of testing a compound for its ability to regulate transcription-activating effects of estrogen and glucocorticoid receptors by assaying for the changes in the level of CAT reporter protein present as a result of contacting cells containing

Art Unit: 1647

GAL4 chimeric estrogen/glucocorticoid receptors and a reporter vector with the compound (pg 200, col 2; Figure 2-3; pg 202, last ¶ of col 2 through 203). Webster et al. discloses GAL4 chimeric estrogen(ER)/glucocorticoid (GR) receptor expression vectors that comprise DNA that encodes amino acids 1-74 or amino acids 1-174 of the DNA binding domain of GAL4 and a region containing the hormone-binding domain of human ER or GR (pg 200, col 2; Figure 5). Webster teaches substituting the native DNA binding domain of PPAR- γ with the DNA encoding the GLA4 DNA binding domain (pg 199-201). Webster et al also teaches a reporter vector that comprises rabbit β -globin promoter, two synthetic 17-mer GAL4 DNA binding sites, and a DNA segment that encodes the CAT reporter protein (pg 200, col 2; Figure 3(A)). Webster et al. teaches cotransfecting HeLa cells with the receptor expression vector and reporter vector and contacting the cells with hormones and anti-hormones wherein the substances caused an increase or decrease in the level of CAT reporter protein (pg 202-203; Figure 3(B)-3(C)).

Webster et al. does not teach contacting cells containing with a compound in the further presence of at least one additional compound that is a receptor agonist or antagonist. Webster et al. also does not teach a GAL4 chimeric PPAR- γ receptor expression vector.

Ikonen et al. teaches co-transfecting CV-1 cells with pSG5-rAR (rat androgen receptor expression vector) and pMMTV-CAT reporter (pg 1360; col 1; pg 1361, last ¶; pg 1362, col 1). Ikonen et al. discloses that after transfection, the cells receive medium supplemented with testosterone and 8-Br-cAMP or Casodex (abstract; Figure 1). Ikonen et al. teaches that the concomitant exposure to 8-Br-cAMP and androgen yielded 2- to 3- fold higher induction than a maximally effective dose of testosterone alone (pg 1360, last ¶; pg 1361, lines 1-2; Figure 2). Ikonen et al. also teaches that the concomitant presence of Casodex with testosterone blunted the

Art Unit: 1647

androgen-elicited activation of the CAT reporter construct to 15-20% of that with testosterone alone (pg 1362, col 1). Ikonen et al. indicates that Casodex behaved like a pure androgen antagonist (pg 1362, col 1). Therefore, Ikonen et al. teaches testing a compound for its ability to regulate transcription-activating effects of a receptor comprising assaying for changes in the level of reporter protein present as a result of contacting cells containing the receptor and reporter vector with the compound and further in the presence of at least one additional compound that is a receptor agonist or antagonist.

Greene et al. teaches the nucleic acid sequence and amino acid sequence of the human PPAR- γ receptor (SEQ ID NOs: 1 and 2). Greene et al. also discloses several domains of PPAR- γ , including the D domain or ligand binding domain (col 14; Figure 1).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the GAL4 chimeric receptor/reporter vector method for testing the transcription activation of a compound as taught by Webster et al. by utilizing the agonist/antagonist testing methods of Ikonen et. al and the PPAR- γ receptor as taught by Greene et al. The person of ordinary skill in the art would have been motivated to make that modification because PPAR- γ is widely expressed in the human hematopoietic system (Greene et al., col 36-39) and the nuclear receptor subfamily to which the PPAR- γ receptor belongs has been shown to regulate the transcription of key enzymes in fatty acid metabolism and may play a role in cancer cell proliferation and differentiation (Greene et al., col 2). The person of ordinary skill in the art reasonably would have expected success because similar methods were already being performed to discover the transcription activating effects of various compounds on

Art Unit: 1647

receptors at the time the invention was made. Therefore, the claimed invention as a whole was clearly *prima facie* obvious over the prior art.

Art Unit: 1647

Conclusion

Claims 16, 18-20, and 43 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148.

The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

Elizabeth C. Kemmerer

BEB
Art Unit 1647
03 September 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER